CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761269Orig1s000

PRODUCT QUALITY REVIEW(S)

Approval

BLA Number: 761269
Assessment Number: 1
Assessment Date: November 12, 2022

Drug Name/Dosage Form	Leqembi (lecanemab-irmb) injection
Strength/Potency	500 mg/5 mL and 200 mg/2 mL vials (100 mg/mL)
Route of Administration	Intravenous infusion
Rx/OTC dispensed	Rx
Indication	Early Alzheimer's Disease (AD; mild cognitive impairment due to AD and mild AD dementia, with confirmed amyloid pathology)
Applicant/Sponsor	Eisai

Product Overview:

Lecanemab-irmb is a recombinant human immunoglobulin gamma 1 (IgG1) monoclonal antibody targeting aggregated soluble and insoluble aggregate forms of amyloid beta (Aβ). It is expressed in a Chinese hamster ovary (CHO) cell line.

Leqembi (lecanemab-irmb) injection is a preservative-free, sterile, clear to opalescent and colorless to yellow solution for intravenous infusion after dilution. It is supplied in single-dose vials available in concentrations of 500 mg/5.0 mL (100 mg/mL) or 200 mg/2 mL (100 mg/mL).

Quality Assessment Team:

Discipline	Assessor	Team Leader	Branch/Division
Drug Substance, Drug Product	Gunther Boekhoudt	Sam Mindaye, Jennifer Swisher	CDER/OPQ/OBP/DBRRIV
Immunogenicity	Jennifer Swisher		
Labeling	Scott Dallas		CDER/OPQ/OBP
DS Facility and Microbiology	Wendy Tan	Zhong Li, QAL, Facilities Maxwell Van Tassell, QAL, Microbiology	CDER/OPQ/OPMA/DBM/BMB1
DP Facility and Microbiology	Esther C. Broner		
Application Team Lead	Jennifer Swisher		CDER/OPQ/OBP/DBRRIV
RBPM	Rabiya Haider, Janell Artis		CDER/OPQ/OPRO/DRBPMI/RBPMB1

Multidisciplinary Assessment Team:

Discipline	Assessor	Office/Division
RPM	Emilios (Andrew) Papanastasiou	CDER/OND/ORO/DRON
Cross-disciplinary Team Lead	Ranjit Mani	CDER/OND/ON/DNI
Medical Officer	Kevin Krudys - Efficacy Deniz Erten-Lyons – Safety	CDER/OND/ON/DNI
Pharmacology/Toxicology	Christopher Toscano, Lois Freed, TL	CDER/OND/ON/DPTN
Clinical Pharmacology	Yifei Zhang/ Bilal AbuAsal, TL	CDER/OTS/OCP/DCPI
Statistics	Tristan Massie/Kun Jin, TL	CDER/OTS/OB/DBI

1. Names:

   a. Proprietary Name: Leqembi

Reference ID: 5099265

b. Trade Name: Leqembi
c. Non-Proprietary Name/USAN: lecanemab-irmb
d. CAS Number: 260393-98-3
e. Common Name: Lecanemab
f. INN Name: Lecanemab
g. Compendial Name: N/A
h. OBP systematic name: MAB HUMANIZED (IGG1) ANTI P05067 (A4_HUMAN) [BAN2401]

Submissions Assessed:

Submission(s) Assessed	Document Date
STN 761269/0001 – Submission of Modules 1, 2, 4, and 5	September 27, 2022
STN 761269/0036 – Submission of Module 3 (completing BLA submission)	May 6, 2022
STN 761269/0039 - Quality/Response to Information Request	May 24, 2022
STN 761269/0048 – Quality/Response to Information Request	June 14, 2022
STN 761269/0049 - Quality/Response to Information Request	June 22, 2022
STN 761269/0056 – Stability Update	July 28, 2022
STN 761269/0068 - Labeling/Container-Carton Draft	September 26, 2022
STN 761269/0075 - Quality/Response to Information Request	October 6, 2022
STN 761269/0081 - Quality/Response to Information Request	October 20, 2022
STN 761269/0084 - Quality/Response to Information Request	October 31, 2022
STN 761269/0088 - Quality/Response to Information Request	November 7, 2022
STN 761269/0090 - Quality/Response to Information Request	November 17, 2022

More detailed assessments of the BLA submission(s), which are not included in this integrated quality assessment, may be requested via a Freedom of Information Act (FOIA) request.

Quality Assessment Data Sheet:

1. Legal Basis for Submission: 351(k)
2. Related/Supporting Documents:

A. DMFs:

DMF #	DMF Type	DMF Holder	Item referenced	Code[1]	Status [2]	Date Assessment Completed	Comments
(b) (4)	III	(b) (4)		3	N/A	N/A	Sufficient leachables and extractables and primary stability data in the BLA.
	III			3	N/A	N/A	
	III			3	N/A	N/A	
	II			3	N/A	N/A	
	II			3	N/A	N/A	
	II			3	N/A	N/A	
	II			3	N/A	N/A	
	III			3	N/A	N/A	

1. Action codes for DMF Table: 1- DMF Assessed; Other codes indicate why the DMF was not assessed, as follows: 2- Assessed previously and no revision since last assessment; 3- Sufficient information in application; 4- Authority to reference not granted; 5- DMF not available; 6- Other (explain under “comments”)

2. Action codes for Status column: Adequate, Adequate with Information Request, Deficient, or N/A (There is not enough data in the application; therefore, the DMF did not need to be assessed.

B. Other documents: IND, Referenced Listed Drug (RLD), or sister application.

Document	Application Number	Description
IND	105081	Investigation of the use of BAN2401 for the treatment or prevention of Alzheimer's Disease. Initially submitted on June 29, 2010.

3. Consults: Dr. Thomas O'Connor (CDER/OTS, FDA emerging technology team) provided consult review on two novel process analytical technology (PAT) elements in the manufacturing process

Discipline/Topic	Date Requested	Status	Recommendation	Assessor
RAMAN spectroscopy for bioreactor glucose control and bio-capacitance probes for cell mass based nutrient feed control	9/23/2022	complete	Approval	Thomas O'Connor

4. Environmental Assessment of Claim of Categorical Exclusion: Acceptable per 21 CFR 25.31(b)

Executive Summary:

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

The Office of Biotechnology Products, OPQ, CDER, recommends approval of STN 761269 for LEQEMBI manufactured by Eisai, Incorporated. The data submitted in this application are adequate to support the conclusion that the manufacture of LEQEMBI is well-controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert.

B. Approval Action Letter Language:

- Manufacturing locations:
    - Drug Substance: Biogen International GmbH, Attisholzstrasse 11, 4542 Luterbach, Switzerland (FEI: 3017081436)
    - Drug Product: Biogen U.S. Corporation, 900 Davis Drive, Research Triangle Park, NC 27709, USA (FEI: 3010164829)

C. Benefit/Risk Considerations:

Leqembi (lecanemab-irmb) is indicated for the treatment of early Alzheimer's disease, an irreversible, progressive neurodegenerative disease. The FDA recognizes the urgent and unmet medical need for effective treatments for Alzheimer's disease and particularly for treatments to

delay, halt, or reverse its pathophysiological processes. Lecanemab received breakthrough designation for this indication on June 21, 2021 and received Fast Track designation on December 20, 2021.

D. Recommendation on Phase 4 (Post-Marketing) Commitments (draft language)

1. Perform a shipping study to confirm validation of the commercial lecanemab drug product shipping conditions and provide the results of your study. The study will include monitoring of temperature during the shipment, testing of pre- and post-shipping samples for product quality (purity by SEC, cSDS reduced and non-reduced, cIEF, sub-visible particles, and potency of lecanemab), and confirmation that the commercial shipping configuration minimizes physical damage to drug product containers.
2. Improve the sensitivity for the current anti-drug antibody (ADA) assay to at least 100 ng/ml in the presence of the trough level of drug expected to be present during sampling. If sensitivity for the current ADA assay cannot be improved, develop and validate an alternative assay with this level of sensitivity. Improve the sensitivity and drug tolerance of the current neutralizing antibody (NAb) assay. If sensitivity and drug tolerance for the current NAb assay cannto be improved, develop and validate an alternative assay with adequate sensitivity and drug tolerance. Include in the assay validation a statistical evaluation of distribution and outlier exclusion for cutpoint samples, selectivity, system suitability specifications for negative and positive controls, and effects of hemolysis. Refer to the 2019 FDA guidance for immunogenicity assays (https://www.fda.gov/regulatory-information/search-fda-guidancedocuments/immunogenicity-testing-therapeutic-protein-productsdeveloping-and-validating-assays-anti-drug), as this document recommends sensitivity in the range of 100 ng/ml or lower.

III. Summary of Quality Assessments:

A. CQA Identification, Risk and Lifecycle Knowledge Management

Table 1: Active Pharmaceutical Ingredient CQA Identification, Risk and Lifecycle Knowledge Management

Type of CQA	Risk	Origin	Control Strategy	Other
Identity*	Safety	Intrinsic to molecule	(b) (4)	
Degree of Clarity and Opalescence	DP Stability	Formulation		
Degree of Coloration				
Protein Concentration	Biological Activity, Safety	Formulation		
Binding to Aβ and signaling through FcγRs	Stability, biological activity, PK/PD	Intrinsic to molecule, (b) (4) and on DP stability		

Type of CQA	Risk	Origin	Control Strategy	Other
			(b) (4)	
Low Molecular Weight Species	Biological Activity, PK/PD, stability	Protein isoforms. (b) (4)		
High Molecular Weight Species and Proteinaceous Sub-visible and Visible Particulates	Biological activity, PK/PD, immunogenicity, safety, stability			
Oxidation, deamidation, glycation, (b) (4)	Biological activity, PK/PD, stability	Protein isoforms. (b) (4)		
Glycosylation: Aglycosylated variants, afucosylated variants (both high-mannose and non-high mannose), galactosylation	Biological activity, PK/PD	Protein isoforms. (b) (4)		
(b) (4)	PK/PD	Protein isoforms. (b) (4)		

Type of CQA	Risk	Origin	Control Strategy	Other
		(b) (4)	(b) (4)	
pH	Stability	Formulation. (b) (4)		

*Not a CQA but testing required by regulatory expectations.
DS - Drug Substance, DP - Drug Product, CE-SDS – Capillary electrophoresis sodium dodecyl sulfate, SE-HPLC – Size Exclusion Chromatography, icIEF – imaged capillary isoelectric focusing, CPP- critical process parameter.

B. Drug Substance [lecanemab-irmb] Quality Summary

CQA Identification, Risk, and Lifecycle Knowledge Management

Table 2: Drug Substance CQA Process Risk Identification and Lifecycle Knowledge Management*.

Type of CQA	Risk	Origin	Control Strategy	Other
(b) (4)	Safety	(b) (4)	(b) (4)	N/A
	Safety	(b) (4)		N/A

*Control strategies for standard drug substance CQAs are as follows: (b) (4)

(b) (4)

- Description: Lecanemab- irmb is a genetically engineered, humanized, full length IgG1 antibody that targets Aβ-aggregates, Aβ-soluble oligomers, and Aβ-insoluble fibrils with selectivity for Aβ protofibrils. The antibody contains two light chains and two heavy chains with a nominal theoretical molecular mass of 149,818 Da. Each light chain contains 219 amino acids while each heavy chain contains 454 amino acids. A total of 32 cysteine residues form 16 total disulfide bonds, four inter-chain and twelve intra-chain. Glycosylation is N-linked to Asn 304 on the heavy chain.

- Mechanism of Action (MoA): Lecanemab-irmb is a human monoclonal antibody targeting Aβ-aggregates, Aβ-soluble oligomers, and Aβ-insoluble fibrils, which are pathophysiological features of Alzheimer's disease. Lecanemab- irmb reduces amyloid plaques that accumulate in the brains of people with Alzheimer's disease through antibody-dependent microglial-mediated phagocytosis.

- Potency Assay: The sponsor uses two potency assays in DS and DP release and stability and has also implemented control over the allowable glycosylation of lecanemab-irmb in order to assure consistent control of potency and safety.

    - Aβ binding assay: This antigen binding ELISA measures the relative binding potency (RBP%) of lecanemab DS and DP binding to amyloid beta (Aβ) compared to the reference standard. Streptavidin-coated microtiter plates are used to capture biotinylated lecanemab antigen, Aβ (1–16), which are recognized by lecanemab DS/DP and reference standard. The capture complex is detected using alkaline phosphatase (AP) conjugated goat anti-human IgG (H+L) and visualized using 4-methylumbelliferyl phosphate (MUP) substrate. The generated fluorescence is measured using a fluorescent plate reader.

    - FcγRIIa binding assay: Binding of lecanemab to FcγRIIa (CD32a) is measured relative to that of the reference standard by Surface Plasmon Resonance (SPR). A Cytiva Series S Sensor Chip CM5 is coated with immobilized anti-His antibody, which in turn captures the His-tagged FcγRIIa receptor. Lecanemab samples are injected and flow over the chip; complex formation is measured as resonance units based on the change in resonance observed using polarized light directed at the chip. The relative response is directly proportional to the amount of lecanemab bound to the FcγRIIa receptor. Results are reported relative to a reference standard and expressed as a relative binding potency.

- Reference Materials: (b) (4)

- Critical starting materials or intermediates: (b) (4)

(b) (4)

- Manufacturing process summary: (b) (4)

(b) (4)

- Container closure: (b) (4)
- Dating period and storage conditions: (b) (4) months at (b) (4) °C

C. Drug Product [lecanemab-irmb] Quality Summary:

Table 3 provides a summary of the identification, risk, and lifecycle knowledge management for drug product CQAs that derive from the drug product manufacturing process and general drug product attributes.

Table 3: Drug Product CQA Identification, Risk, and Lifecycle Management

Type of CQA	Risk	Origin	Control Strategy	Other
Sterility (contaminant)	Safety, Purity, and Efficacy	Manufacturing process, failure of the container closure integrity	(b) (4)	
Endotoxin (contaminant)	Safety, Purity	Raw materials, manufacturing process		
Container closure integrity (Sterility assurance)	Safety (Sterility assurance)	Breach during manufacture or storage		
Appearance (Clarity and Color)	Product stability	Formulation		
Visible Particles	Safety and immunogenicity	Formulation, accidental through process or environment.		
Subvisible Particles (b) (4)				
Osmolality	Product stability, patient comfort	Formulation		
Extractable volume	Inaccurate dosing	Filling/storage		
Identity	Medication error	Manufacturing Process		
Protein Concentration	Inaccurate dosing	Manufacturing process		

- Potency and Strength: Vial: 200 mg/2 mL (100 mg/mL) or 500 mg/5 mL (100 mg/mL)

- Summary of Product Design: LEQUEMBI (lecanemab-irmb) injection is supplied in a (b) (4) glass vial closed with a stopper and seal with a flip-off cap. The vials each contain a single dose of the drug product. Different color flip-off buttons are used to differentiate different dose presentations.

- List of Excipients: 1.2 mmol/L histidine (0.18 mg/mL), 23.8 mmol/L histidine hydrochloride monohydrate (4.99 mg/mL), 200 mmol/L arginine hydrochloride (42.13 mg/mL), 0.05% (w/v) polysorbate 80 (0.50 mg/mL), and Water for Injection (USP) at pH 5.0.

- Reference Materials: Same as lecanemab-irmb DS.

- Manufacturing process summary: Manufacturing process summary: LEQEMBI DP is manufactured at Biogen U.S. Corporation, 900 Davis Drive, Research Triangle Park, NC 27709, USA. DP manufacturing process (b) (4)

(b) (4)

- Container closure: Lecanemab DP container closure system consists of 6 mL (b) (4) glass vials with 20 mm rubber stopper and silver aluminum crimp seal with plastic flip-off button.

- Dating period and storage conditions: 12 months at 2 to 8°C

D. Biopharmaceutics Considerations: None

E. Novel Approaches/Precedents: None

F. Any Special Product Quality Labeling Recommendations:

- Store LEQEMBI vials in the refrigerator at 2°C to 8°C (36°F to 46°F) until time of reconstitution.
- Dilute required amount of LEQEMBI in 250 mL 0.9% sodium chloride solution for injection.
- After dilution, immediate use is recommended. If not administered immediately, store LEQEMBI refrigerated at (2°C to 8°C [36°F to 46°F]) for up to 4 hours, or at room temperature up to 30°C (86°F) for up to 4 hours. Do not freeze.
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G. Establishment Information:

Overall Recommendation:					
DRUG SUBSTANCE					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
DS Manufacture,	Biogen International GmbH (Biogen SOL)	3017081436			

QC testing, DS storage	Attisholzstrasse 11 , Luterbach, Switzerland, 4542		Approve based on inspection	4-item 483 was issued	Approve based on inspection
In-process testing (adventitious viruses, mycoplasma)	(b) (4)		N/A	N/A	Approve based on previous history
QC Testing (b) (4)	Eisai Co. Ltd. 1, Kawashimatakehaya-Machi, Kakamigahara, Gifu, Japan, 5016024	3004967045	Approve based on inspection	2-item 483 was issued	Approved based on inspection
QC testing	PPD Development 8551 Research Way, Suite 90, Middleton, WI 53562 USA	2129896	N/A	N/A	Approve based on previous history
Storage of MCB, WCB	(b) (4)		N/A	N/A	No evaluation necessary
Storage of MCB and WCB			N/A	N/A	No evaluation necessary
Storage of DS			N/A	N/A	No evaluation necessary
DRUG PRODUCT					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
Drug Product Manufacture, (b) (4)	Biogen U.S. Corp. 900 David Dr. Research Triangle Park, NC 27709 USA	3010164829	Approve based on inspection	N/A	Approve based on inspection
QC testing	PPD Development, L.P. 8551 Research Way, Suite 90 Middleton, WI 53562 USA	2129896	N/A	N/A	Approve based on previous history
Bulk Drug Product storage	(b) (4)		N/A	N/A	No evaluation necessary
Labeling, Secondary Packaging	Packaging Coordinators 3001 Red Lion Rd. Philadelphia, PA 19114 USA	1000522077	N/A	N/A	No evaluation necessary
Labeling, Secondary Packaging	Pharma Packaging Solutions, LLC	3002763532	N/A	N/A	No evaluation necessary

H. Facilities:

1. This pre-license inspection (PLI) of the biologics drug substance (DS) manufacturer, Biogen International GmbH (Biogen SOL; FEI: 3017081436) in Luterbach, Switzerland was conducted from 3/21/2022-3/29/2022 under eNSpect Operation ID #219604. The inspection covered (b) (4) Based on inspection findings and review of the Form FDA 483 and the submitted 483 responses, OPMA/DBM recommends approval of the facility. Refer to CMS# 449251.

2. The PLI of the drug product manufacturing facility at Biogen Research U.S. Corporation, Research Triangle Park, North Carolina, was conducted on 8/22/2022-8/26/2022 under eNSpect Operation ID #226430. The manufacturing areas covered (b) (4) . Based on inspection findings and review of the Form 483 and the submitted 483 responses, OPMA/DBM recommends approval of the facility. Refer to CMS# 473611.

I. Lifecycle Knowledge Management:

a. Drug Substance:

i. Protocols approved:
   1. Stability protocols for (b) (4) (Section 3.2.S.2.3)
   2. Concurrent at-scale lifetime validation protocols (b) (4) Section 3.2.S.2.5)
   3. Stability protocols for (b) (4) (Section 3.2.S.5)
   4. Post-approval annual stability protocol for drug substance with shelf-life extension (3.2.S.7.2)

ii. Outstanding assessment issues/residual risk:
   None

iii. Future inspection points to consider:
   None

b. Drug Product

i. Protocols approved:
   Post-approval annual stability protocol for drug product with shelf-life extension (3.2.P.8.2)

ii. Outstanding assessment issues/residual risk:
   None

iii. Future inspection points to consider:
   None

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/s/

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